Descriptive Models and Radiation Risk Assessment

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What is a descriptive model?

- **Function that relates risk (relative or absolute) to dose and factors that might modify risk**
- **Factors might include sex, age at exposure, attained age, time since exposure, smoking, etc.**
- **Models developed by analyzing data from epidemiologic studies**

Why do we need descriptive models?

- **Increase our understanding of radiation carcinogenesis**
- **Radiation risk assessment**

Risk Assessment Examples

- **NRC/NAS: BEIR Reports (Biologic Effects of Ionizing Radiation)**

  BEIR V (1990): Low levels of low-LET radiation

  BEIR VI (1999): Radon

  BEIR VII (2004?): Low levels of low-LET radiation

- **UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation)**

  UNSCEAR (2000): Includes risk estimates

- **NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables (2003)**

Cancer Endpoints

- All cancer
- All solid cancer
- Leukemia
- Other site-specific cancers

Descriptive modeling

- Evaluate dose-response relationship
  - Shape of dose-response
  - Quantify risk as a function of dose
- Evaluate patterns of risk by
  - sex
  - age at exposure
  - time since exposure
  - attained age

Shape of dose-response

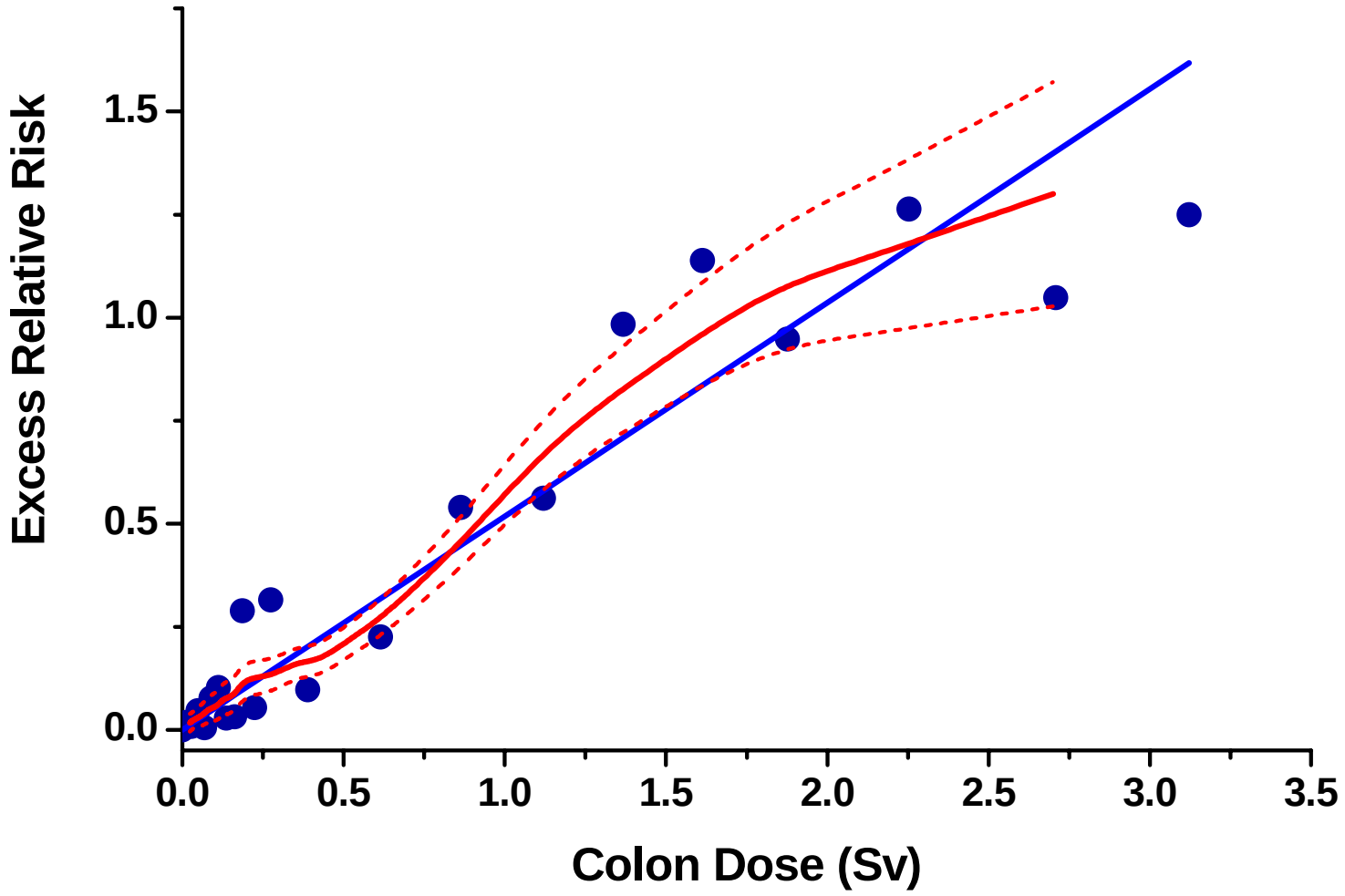
- **Often start by evaluating linear-quadratic functions**

$$f(d) = \alpha\, d + \beta\, d^2$$

- **Most epidemiologic data reasonably well described by linear functions**

- **Special methods have been used to evaluate low-dose portion of A-bomb survivor data**

Solid Cancer Dose Response



(LSS Report 13, Preston et al, 2003)

Patterns of Risk

Excess Relative Risk (ERR) Model

$\lambda(s,a,b)\,[1 + \mathbf{ERR(d,s,e,a,t)}]$

Excess Absolute Risk (EAR) Model

$\lambda(s,a,b) + \mathbf{EAR(d,s,e,a,t)}$

where λ denotes the background rate at zero dose,

d = dose; s = sex; a = attained age; b= birth year

e = age at exposure; and t = time since exposure.

Examples for today's talk

- **A-bomb survivor mortality data (LSS Report 13; Preston et al. 2003)**
  - **Solid cancers**
  - **Leukemia**
  - **Site-specific cancers**
- **Lung cancer risks in Mayak workers**
- **Lung cancer following Hodgkin lymphoma (Gilbert et al. 2002)**

Data Used for Models in Use Today

Low-LET radiation:

- **All solid cancers: A-bomb survivors**
- **Leukemia: A-bomb survivors (patients treated for ankylosing spondylitis)**
- **Breast cancer risk: A-bomb survivors and medically exposed cohorts**
- **Thyroid cancer risk: A-bomb survivors and medically exposed cohorts (pooled analysis)**
- **Other specific cancers: Primarily A-bomb survivors (a few exceptions)**

Radon: Lung cancer: Underground miners

(pooled analysis of 11 cohorts)

Strengths of A-bomb Survivor Study for Use in Risk Assessment

- Large population size
- Useful range of doses
- Whole body exposure
- All ages and both sexes
- Long term follow-up for both mortality and cancer incidence
- Well-characterized dose estimates for individual study subjects

RERF Solid Cancer Models

Recent past:

Simple model: ERR = β_s d

Age-at-exposure model: ERR = β_s d exp(γ e)

UNSCEAR (2000):

Age at exposure model: ERR = β_s d exp(γ e)

Attained age model: β_s d a^k

- **Linear function of dose**
- **Modification variables: s = sex , e = age at exposure,**
  a = attained age

RERF Solid Cancer Models

Current RERF model:

$$ERR(d,s,e,a) \text{ or } EAR(d,s,e,a)$$

$$= \beta_s \, d \exp(\gamma \, e) \, a^{\eta}$$

- **Linear function of dose**
- **Risk depends on sex (s), age at exposure (e), and attained age (a)**
- **Models for both ERR and EAR developed**

RERF Solid Cancer Models

Results from Report 13 (mortality 1950-97)

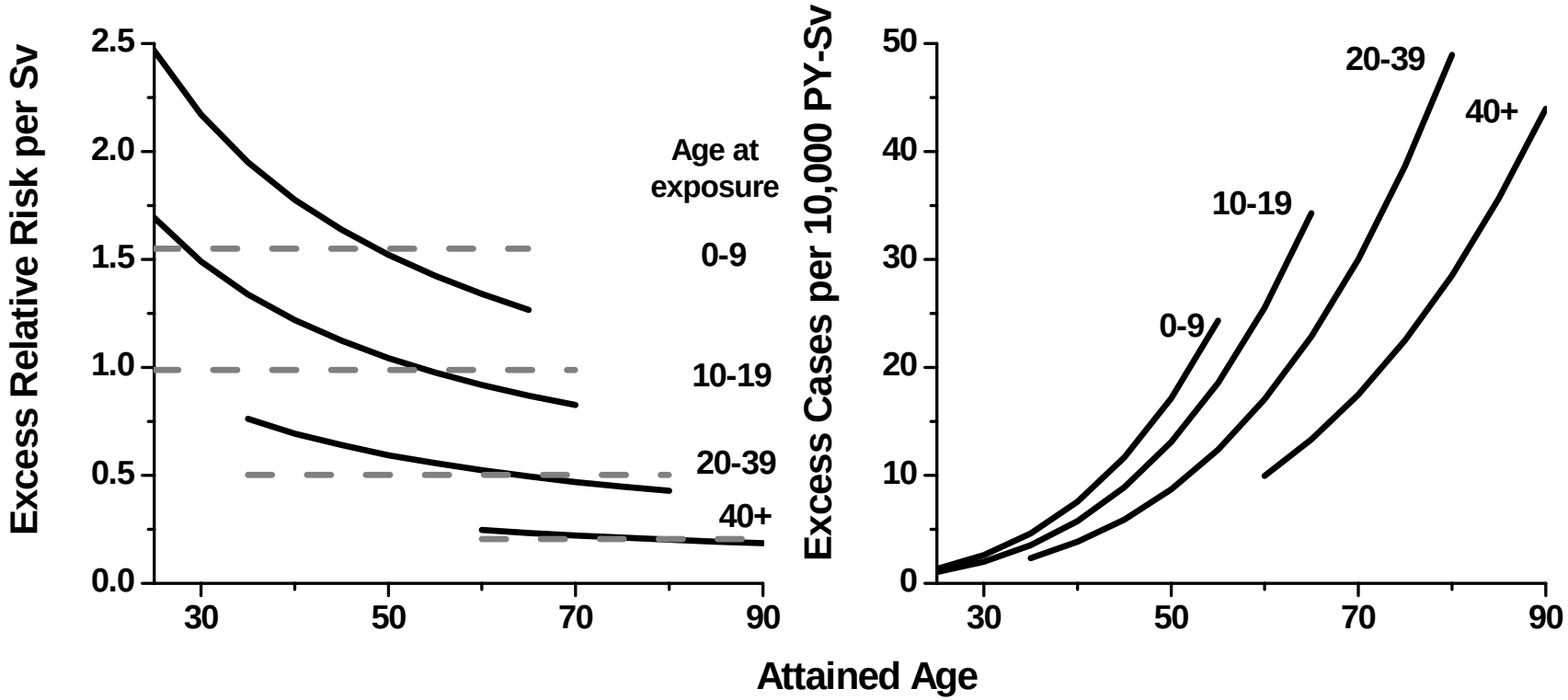
$$ERR(d,s,e,a) = \beta_s \, d \exp(-0.038 \, e) \, a^{-0.7}$$

$$EAR(d,s,e,a) = \beta_s \, d \exp(-0.027 \, e) \, a^{3.7}$$

e is age at exposure in years

a is attained age in years

Solid Cancer: ERR and EAR by Attained Age

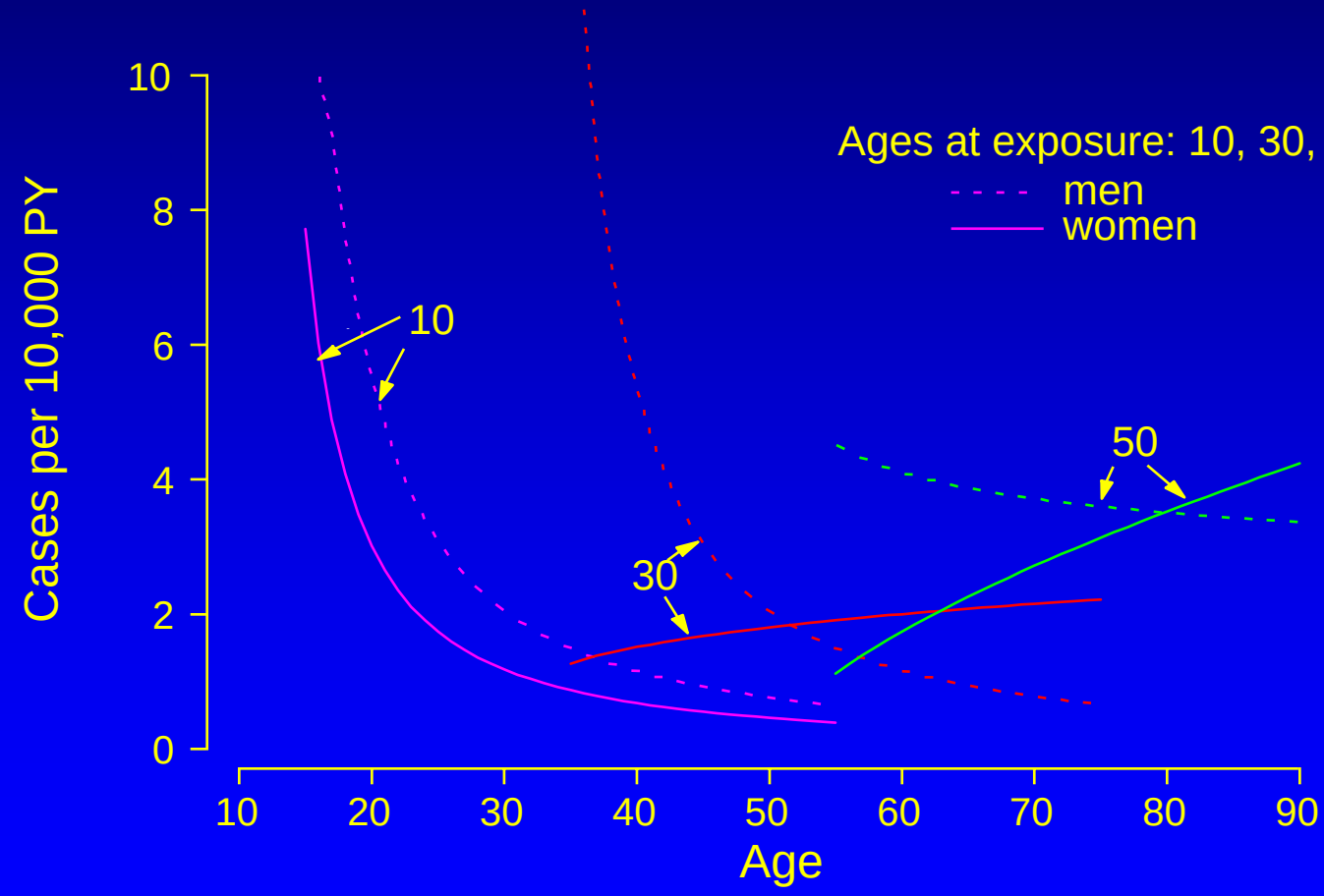


(LSS Report 13, Preston et al, 2003)

Modeling Leukemia Risks

- **Linear-quadratic function needed to describe leukemia risks**
- **RERF has emphasized EAR models (used by UNSCEAR)**
- **BEIR V and NCI/CDC used ERR models**
- **Complex dependencies on sex, age at exposure, and time since exposure**

Leukemia Excess Absolute Risk (1 Sv)



(Pierce et al, 1996)

Modeling Leukemia Risks

NCI/CDC (Radioepidemiological Tables 2003)

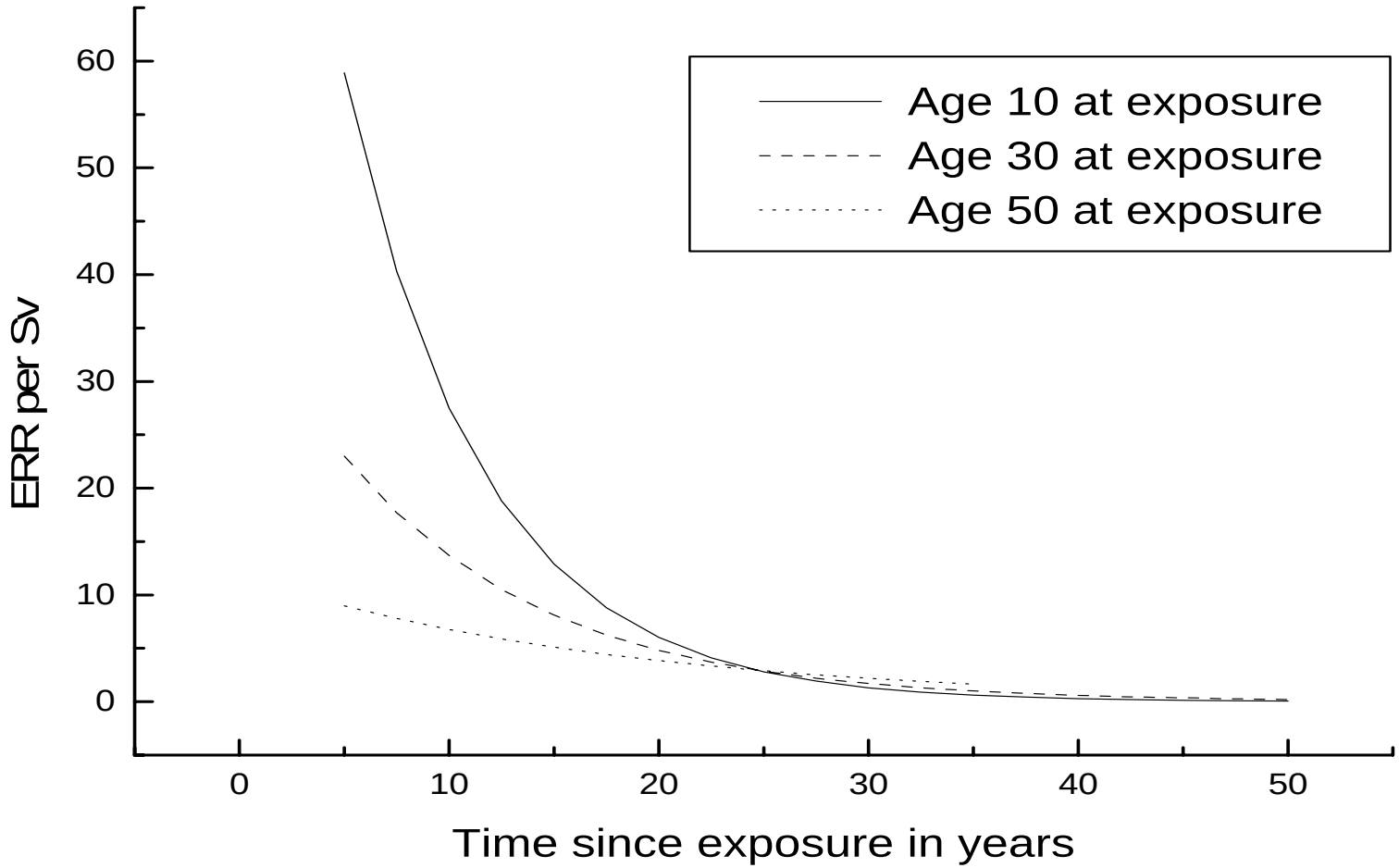
ERR model for describing leukemia risks in A-bomb survivors:

$$ERR(d,s,e) = \beta\, d\, (1 + \theta d)\, \exp[\gamma\, e + \eta\, t + \delta\, e\, t]$$

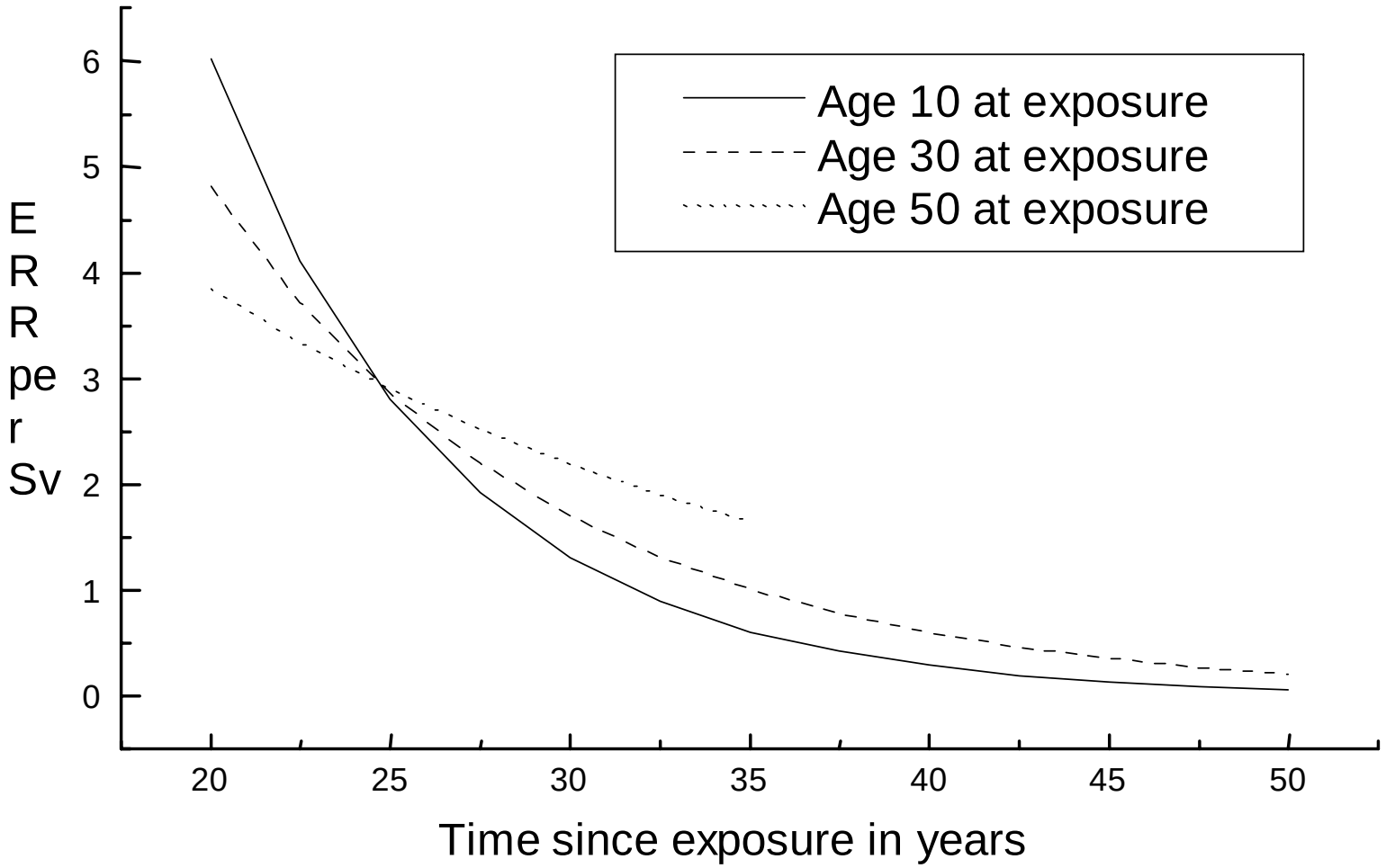
e is age at exposure;

t is time since exposure

Leukemia ERR model (NIH 2003)



Leukemia ERR model (NIH 2003)



Estimates for Cancers of Specific Sites

- Many exposures of interest involve selective irradiation of various tissues
  - Mammography (breast)
  - I-131 (thyroid)
- Probability of causation
- For many cancer sites, A-bomb survivors are main source of information

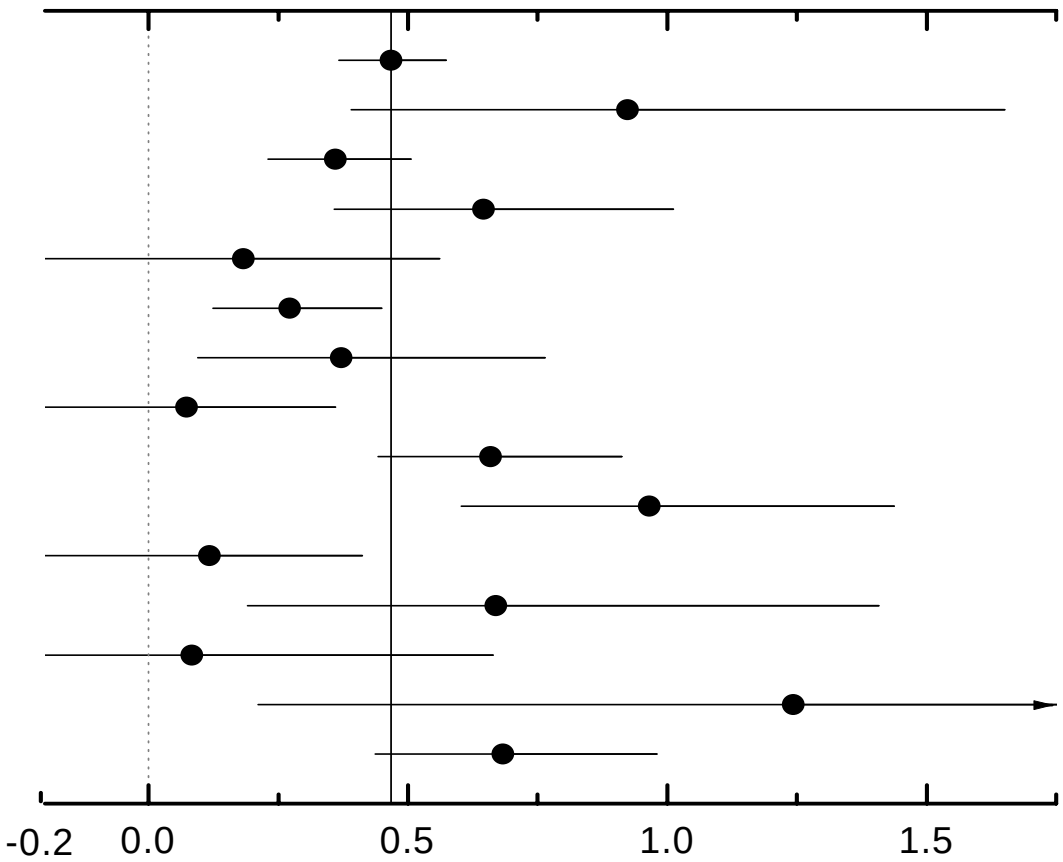
A-bomb survivor data: Site-specific Cancers

$$\text{ERR or EAR} = \beta_s \, d \exp[\gamma \, e] \, a^{\eta}$$

- For many cancer sites, parameter estimates are imprecise, especially for modifying effects (γ and η)
- A possible approach: Use estimates of γ and η based on the combined category of all solid cancers unless there is evidence that γ and η differ from these values
- This general approach used in analyses of A-bomb survivor mortality data (Pierce et al. 1996; Preston et al. 2003), UNSCEAR (2000), and NCI/CDC (2003)

Site-specific ERRs per Sv for person exposed at age 30 at attained age 70

--	Deaths	P-values
All solid cancers	9335	P<0.001
Esophagus	291	P<0.001
Stomach	2867	P<0.001
Colon	478	P<0.001
Rectum	370	P=0.14
Liver	1236	P<0.001
Gall bladder	328	P=0.007
Pancreas	407	P=0.29
Lung	1264	P<0.001
Breast	275	P<0.001
Uterus	518	P=0.20
Ovary	136	P=0.004
Prostate	104	P=0.42
Bladder	150	P=0.02
Other solid	911	P<0.001



(LSS Report 13, Preston et al, 2003)

Modeling the Epidemiological Data: Site-Specific Cancers

$$\text{ERR or EAR} = \beta_s \, d \exp[\gamma \, e] a^{\eta}$$

- Preston et al. (2003) modeled cancer mortality for cancers of the stomach, colon, liver, lung, female breast and all other solid cancer as a group.
- Patterns with age at exposure and attained age generally similar

Exceptions:

- ERR for colon cancer decreased more rapidly with attained age
- EAR for breast cancer showed larger age at exposure effect
- EAR for lung cancer increased more rapidly with attained age

Example 2: Lung Cancer Risks in Mayak Workers

- Estimate risks from protracted external exposure
- Estimate risks from exposure to plutonium

$$\text{ERR or EAR} = [\beta_{s,ext} D_{s,ext} a^{\gamma ext} + \beta_{s,plu} D_{s,plu} a^{\gamma plu}]$$

D_{ext} = external dose in Gy;

D_{plu} = lung dose from plutonium in Gy;

a = attained age in years

Lung Cancer Risks in Mayak Workers

ERR or EAR

- **Linear functions of external and internal dose**

- **Allow for dependencies on gender and attained age**

Parallel analyses: Mayak workers and A-bomb survivors

- Conducted analyses of A-bomb survivor lung cancer mortality data 1950-97
- Restricted to survivors exposed between ages 15 and 60

Example 3: Lung cancer following Hodgkin disease

Investigate interaction of 3 exposures

Exposure	Measure
Radiation	Dose to site of lung tumor
Alkylating agents (AA)	Number of cycles (cyc)
Smoking	Pack-years (pks)

Lung cancer following Hodgkin disease: Some candidate models

I. Multiplicative interaction for all exposures:

$$(1 + \beta_{smk}\,\text{pks})(1 + \beta_{rad}\,\text{dose})(1 + \beta_{AA}\,\text{cyc})$$

II. Additive interaction for all exposures:

$$(1 + \beta_{smk}\,\text{pks} + \beta_{rad}\,\text{dose} + \beta_{AA}\,\text{cyc})$$

III. Multiplicative for smoking and treatment: additive for radiation and alkylating agents

$$(1 + \beta_{smk}\,\text{pks})(1 + \beta_{rad}\,\text{dose} + \beta_{AA}\,\text{cyc})$$

Lung cancer following Hodgkin disease:

Also evaluated more general models:

Example:

$(1 + \beta_{smk}\, pks)\,(1 + \beta_{rad}\, dose + \beta_{AA}\, cyc + \gamma\, dose*cyc)$

$\gamma = 0$ **yields Model III**

$\gamma = \beta_{rad}\, \beta_{AA}$ **yields Model I**

$(1 + 0.15\, dose + 0.75\, cyc + .001\, *dose*cyc)$

Nearly identical fit to Model III

Improved fit over Model I (p = .017)

Lung cancer following Hodgkin disease

Compared the fits of several models.

Conclusions:

- **Interaction of radiation and alkylating agents almost exactly additive; could reject multiplicative model**
- **Interaction of radiation and smoking compatible with multiplicative relationship; could reject additive model**
- **Model III described data well**

Pooled Analyses

- **Parallel Analyses: Fit similar models to data from individual studies**

- **Analyze combined data**
  - **Determine extent to which common parameters are appropriate (main effects, modifying factors)**
  - **Develop models that adequately describe data**

Pooled Analyses

Models based on data from several studies --

- **Lung cancer in radon-exposed miners and estimation of risk from indoor exposure (Lubin et al. JNCI 1995). Also BEIR VI.**
- **Thyroid cancer after exposure to external radiation: A pooled analyses of seven studies (Ron et al. Radiat. Res. 1995)**
- **Radiation effects on breast cancer risk: A pooled analysis of eight cohorts (Preston et al. 2002)**

Errors in Dose Estimates Used in Epidemiologic Analyses

- Most past analyses have not accounted for such errors
- Complex methods often required to take errors into account
- Increasingly, errors are being evaluated and considered in dose-response analyses
- A-bomb survivors: Recent analyses calibrated to adjust for random errors

Possible Effects of Not Accounting for Errors in Dose Estimates

- **Bias in estimated risk coefficients**
- **Biased comparisons across subgroups and studies**
- **Distortion of the shape of the dose-response function**
- **Underestimation of uncertainty**

Accounting for Errors in Dose Estimates

- **Requires good understanding of error structure**
- **Systematic errors require different treatment than random errors**
- **Classical errors require different treatment than Berkson errors**
- **Requires lots of communication between dosimetrists and statisticians**

Use of Models for Radiation Risk Assessment

- **Have developed models based on epidemiologic data**

  (A-bomb survivors, for example)

- **Apply model to population/exposure situation for which risk estimates desired**

Examples where radiation risk estimates needed

- Risk from exposure received as a result of mammography
- Risk from residential exposure to radon
- Risk from I-131 exposure from atmospheric nuclear tests
- Risk from pediatric CT examinations

Example: Mammography

- **What is the added risk of breast cancer for a woman who begins annual examinations at age 40? At age 50?**
- **What is the added risk of breast cancer death for these situations?**
- **How many breast cancers deaths occur each year as a result of mammography?**
- **How does this compare with the number of deaths prevented?**

Radiation Risk Assessment

- **Radiation literature periodically reviewed and evaluated by several national and international committees**
- **Many of these committees develop and recommend models for estimating risks**
- **These models can then be applied to specific exposure situations**

Radiation Risk Assessment

- **NRC/NAS: BEIR Reports (Biologic Effects of Ionizing Radiation)**
- **UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation)**
- **NCRP (National Committee on Radiation Protection and Measurements**
- **ICRP (International Commission on Radiation Protection)**

Measures of Risk

- **Lifetime risk: Risk of developing (fatal) cancer over exposed person's lifespan**
- **Years of life lost per excess fatal cancer**
- **Probability of causation**

Estimating Lifetime Risk

- Starting with exposure at age e, follow the population forward in time allowing attrition as the population ages
- Apply age-specific ERR (EAR) to estimate excess cancers occurring at each age (a)
- Sum (integrate) over all ages to obtain risk for persons exposed at age e (R_e)
- For population of mixed exposure ages, can take weighted average of the R_e

Estimating Lifetime Risk: Needed information

- **Models for ERR and EAR**
- **Data on exposed population of interest**
  - **Age-sex composition**
  - **Survival (life-table) data**
  - **Age- and sex-specific baseline rates for cancer(s) of interest (for ERR models)**

Issues in Estimating Lifetime Risk

- **Extrapolation from high to low doses and dose rates**
- **Extrapolation beyond period for which follow-up data are available (especially for those young at exposure)**
- **Extrapolation from Japanese A-bomb survivors to other populations**
  - **Baseline risk may differ**

A-bomb survivor follow-up

Age at exposure	Age in 1997
10	62
30	82
50	102

- Follow-up complete except for youngest survivors
- Extrapolation beyond follow-up period much less of a problem now than in the past

Applying Risk Model : Assumptions

- **Extrapolation from high to low doses and dose rates**
- **Extrapolation beyond period for which follow-up data are available (especially for those young at exposure)**
- **Extrapolation from Japanese A-bomb survivors to other populations**
  - **Baseline risk may differ**

"Transporting" Risks from Japan to Other Countries

- **Baseline risks for Japan and and other countries differ**
- **To what extent do radiation risks depend on baseline risks?**

Cancer Incidence in US and Japan (Males)

	US	Japan	Ratio
All	380	305	1.2
Stomach	8.4	77	0.11
Colon	29	29	1.0
Liver	3.5	39	0.09
Lung	66	41	1.6
Bladder	22	12	1.8

Source: Cancer Incidence in Five Continents, 1997

Cancer Incidence in US and Japan (Females)

	US	Japan	Ratio
All	280	185	1.5
Stomach	3.5	34	0.10
Colon	22	17	1.3
Liver	1.3	9.8	0.13
Lung	34	12	2.8
Breast	89	30	3.0
Bladder	5.9	2.6	2.3

Source: Cancer Incidence in Five Continents, 1997

Approaches for Transporting Risks from Japan to Other Countries

- **Absolute risk transport (AR):** Absolute risks the same for Japan and US (BEIR III)
- **Relative risk transport (RR):** Excess relative risks the same for Japan and US (BEIR V)
- Intermediate (EPA, NCI/CDC)
- Both (UNSCEAR)

Model for transporting risks: How do we decide?

- **Consider factors responsible for differences in baseline risks**
  - **Additive interaction with radiation supports absolute risk transport**
  - **Multiplicative interaction with radiation supports relative risk transport**
- **Likely more than one factor**
  - **Intermediate model**

Model for transporting risks: How do we decide?

- **Biological considerations (initiation/promotion)**
- **Compare epidemiologic data on Caucasian populations and A-bomb survivors**
  - **If ERRs comparable, use relative risk transport**
  - **If EARs comparable, use absolute risk transport**
- **Evaluate interaction of radiation and factors that contribute to differences in baseline risks**

Model for transporting risks: How do we decide?

Use epidemiologic data on medically exposed Caucasian populations

- **Relevant data limited**
- **Statistical uncertainties often large**
- **Almost always differences other than nationality/ethnicity/race**
  - **Many medical exposures involve high therapeutic doses (cell-killing may lead to lower risk estimates)**
  - **Doses often fractionated**

Model for transporting risks: Breast cancer

- Data on Caucasian women have played key role
  - Massachusetts tuberculosis fluoroscopy patients
  - Rochester infant thymus irradiation cohort
  - New York women treated with radiation for mastitis
- Conduct parallel analyses of A-bomb survivors and Caucasian women
  - Land et al. (1980) found that EAR more comparable than ERR, supporting the absolute risk transport model
  - Confirmed in recent combined analysis by Preston et al. (2002)
- Note: Other differences
  - Fractionation of exposure
  - Photon energy

Model for transporting risks: Breast cancer

- Preston et al. (2002) conducted combined analyses of breast cancer incidence data on several cohorts

- ERR and EAR models developed based on
  - A-bomb survivors
  - Massachusetts tuberculosis fluoroscopy patients
  - Rochester infant thymus irradiation cohort

ERR model based on combined analysis

$$\text{ERR per Gy} = B\,(a/50)^{-2}$$

where B = 2.1 for A-bomb survivors

B = 0.74 for Caucasian cohorts

Preston et al. 2002

EAR model based on combined analysis

EAR per 10^4 woman-year-Gy =

$$9.9 \exp[-.04(e - 25)](a/50)^{\eta}$$

- **Same model fit both A-bomb survivor and Caucasian women**
- **EAR depended on both age at exposure (e) and attained age (a) (η = 3.5 before age 50; 1.1 after age 50)**

Preston et al. 2002

UNSCEAR 2000 Risk Models

- Risk estimates obtained for
  - China
  - Japan
  - Puerto Rico
  - United Kingdom
  - United States
- Used demographic and baseline risks from these countries

UNSCEAR 2000 Approach

Age at exposure model: ERR = β_s d exp[γ e]

Attained age model: ERR = β_s d a^k

s = sex; e = age at exposure; a = attained age

(Attained age model gives lower lifetime risks)

Calculated lifetime risks using both

relative risk transport (RR) and

absolute risk transport (AR)

UNSCEAR 2000 Lifetime Risk Estimates (%) of Solid Cancer Mortality Following Exposure of 1 Sv

	Males		Females	
	RR	AR	RR	AR
China	4.9	5.3	7.1	6.8
Japan	6.2	6.2	8.5	8.5
Puerto Rico	4.4	6.1	7.9	8.2
UK	6.6	6.7	13.5	9.1
US	6.2	5.4	12.4	7.6

Based on attained age model

UNSCEAR 2000 Lifetime Risk Estimates (%) of Cancer Incidence Following Exposure of 1 Sv (Males)

	RR	AR
Esophagus	0.2	0.4
Stomach	0.2	1.5
Colon	1.1	1.2
Liver	0.1	2.1
Lung	2.9	2.0
Breast	--	--
Bladder	0.4	0.3
Other solid cancer	6.8	2.5

UNSCEAR 2000 Lifetime Risk Estimates (%) of Cancer Incidence Following Exposure of 1 Sv (Females)

	RR	AR
Esophagus	0.1	0.1
Stomach	0.1	1.6
Colon	1.9	1.7
Liver	0.1	0.7
Lung	7.5	3.5
Breast	13.6	4.9
Bladder	1.0	1.2
Other solid cancer	2.2	1.4

ICRP 1991 Risk Estimate

- **ICRP (1991) recommended a cancer mortality risk estimate of 5% per Sv for exposure to a population at all ages at low dose-rates**
- **Based on consideration of lifetime risks for China, Japan, Puerto Rico, UK, and US and reducing linear estimate by DDREF of 2**
- **Does not take account of specific characteristics of exposed population**
- **Simple summary measures can be useful, and at least indicate the order of magnitude of the risk**

Contribution of Various Organs to Total Cancer Mortality (ICRP 1991)

Organ	% per Sv	Organ	% per Sv
Bladder	0.30	Esophagus	0.30
Bone marrow	0.50	Ovary	0.10
Bone surface	0.05	Skin	0.02
Breast	0.20	Stomach	1.10
Colon	0.85	Thyroid	0.08
Liver	0.15	Remainder	0.50
Lung	0.85	Total	5.00

Uncertainties in Lifetime Risk Estimates

- Statistical uncertainties
- Errors in epidemiological data
  - dose estimates, health endpoints
- Extrapolation from high to low doses and dose rates
- Extrapolation beyond period for which follow-up data are available (especially for those young at exposure)
- Extrapolation from Japanese A-bomb survivors to other populations